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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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MORRISON & FOERSTER LLP
755 PAGE MILL RD
PALO ALTO, CA 94304-1018

EXAMINER	
KERR, KATHLEEN M	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/957,483	ARSLANIAN ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40 and 42-65* is/are pending in the application.

4a) Of the above claim(s) *1-39 and 42-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40 and 48-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/11/02 12/12/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. In response to the previous Office action, a written restriction requirement (mailed on September 9, 2003), Applicants filed an amendment and response received on October 29, 2003. Said amendment amended Claim 40, cancelled Claim 41, and added new Claims 48-65. Thus, Claims 1-40 and 42-65 are pending in the instant Office action.

Election

2. Applicants' election without traverse of Group IV, Claims 40-41, in a paper received October 29, 2003 is acknowledged. New claims 48-65 are drawn to the elected invention. Claims 1-39 and 42-47 are withdrawn from consideration as non-elected inventions; Claims 40 and 48-65 will be examined herein.

Applicants are reminded to consider inventorship of the elected Group, particularly in light of the inventorship of other priority applications noted below, that disclose the claimed invention.

Priority

3. The instant application requests priority to International Application PCT US01/13793 filed on April 26, 2001; said priority is granted. This International Application also claims priority to several U.S. provisional and non-provisional applications; said priority is also granted. However, due to the disclosures of said U.S. applications relative to the elected invention being only in applications 09/825,876 (April 3, 2001) and 60/269,020 (February 13, 2001), an earliest effective filing date of February 13, 2001 is granted for the pending claims.

Information Disclosure Statement

4. The information disclosure statements filed on June 11, 2002 and December 12, 2003 have been reviewed, and their references have been considered as shown by the Examiner's initials next to each citation on the attached copies.

Compliance with the Sequence Rules

5. By virtue of the sequence listing filed on February 19, 2002, the instant application now fully complies with the sequence rules.

Objections to the Specification

6. The specification is objected to because the title is not descriptive. A new title is required that is clearly indicative of the invention to which the elected claims are drawn (see M.P.E.P. § 606.01). The Examiner suggests the following new title:

--Methods of Purifying Epothilone from Cells Using Resins and Solid Phase Extraction--

7. In the specification, the Abstract is objected to for not completely describing the disclosed subject matter (see M.P.E.P. § 608.01(b)). It is noted that in many databases and in foreign countries, the Abstract is crucial in defining the disclosed subject matter, thus, its completeness is essential. The Examiner suggests the inclusion of native source species for epothilone, *S. cellulosum*. The Examiner also suggests inclusion of a description of the method steps for epothilone purification, such as found on page 135, paragraph 365. Completeness of the abstract is required.

8. The specification is objected to for being confusing. On page 137, paragraph 371, a step "3b" is referred to, but not such step is found in the description. Clarification is required.

9. The amendment filed September 19, 2001 is objected to under 35 U.S.C. § 132 because it introduces new matter into the disclosure. 35 U.S.C. § 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the incorporation by reference of the priority documents. While the preliminary amendment was filed on the day of filing, it is not referred to in the declaration and, thus, is not considered part of the specification as originally filed.

Applicant is required to cancel the new matter in the reply to this Office Action or to recite clear support for the amendment as filed.

Objections to the Claims

10. Claim 63 is objected to for a typographical error. The word "preformed" is misspelled; the correct spelling is ---performed---. Correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 49, 50, 62, and 65 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claims 49, 62, and 65, the term "about" is used to describe a methanol concentration or the particle distribution of an extraction resin. In each case, the

metes and bounds of the adjective "about" are unclear as based on the specification. For the methanol concentration, percentages of 100% (on page 110, for example) to 80% (on page 137, for example) are noted in the specification; however, it is unclear if 80% is "about 100%". For the micron size, the only mention is found on page 135, paragraph 364, wherein no other numbers besides 40 and 60 are mentioned to assist one of skill in the art to be able to ascertain the variation of "about 40" and "about 60". On both these points, clarification is required.

12. Claim 50 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 50 refers to "said resin"; however, the combination of Claim 40 and Claim 49 include both an adsorber resin and a C18 resin. The resin to be eluted with methanol in Claim 50 is unclear. Clarification is required.

13. Claim 52 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear if epothilone D is the only epothilone produced in the claimed method. The article "the" implies as much; however, the specification does not teach purification of pure epothilone D. Clarification is required.

14. Claim 65 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The metes and bounds of "exogenous trace element solution" are wholly unclear. Must the trace elements that are added, as implied by exogenous, not be found in the *M. xanthus*

cell natively? Exactly what kind of materials are these? The specification, while supporting the language used, does not define the terms. Trace metals are mentioned on page 103, paragraph 268; but this limitation cannot be read into the claims. Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 49 and 65 are rejected under 35 U.S.C. § 112, first paragraph, new matter, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The limitation of using a column of "**about** 40 microns to **about** 60 microns" (emphasis added) is not supported in the specification as originally filed. The exact range of 40-60 is supported on page 135, paragraph 364. Applicant is required to cancel the new matter in the reply to this Office Action or to recite clear support for the amendment as filed.

16. Claims 40, 48-59, and 62-65 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to methods using a hydrophobic adsorber resin that adsorbs epothilone wherein said resin is described only by function and not by structure.

To satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for claimed use of a genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed.

In the specification, a limited genus of a hydrophobic adsorber resin that bind epothilones, XAD resins, is described. No examples of other hydrophobic adsorber resin that bind epothilone are discussed. The instant claims are drawn to a *subgenus* of all hydrophobic adsorber resins that do bind epothilone. The specification does not describe, using structural terms, hydrophobic adsorber resins that bind epothilone to the exclusion of hydrophobic adsorber resins that do not bind epothilone. Thus, the methods using the claimed subgenus of hydrophobic adsorber resins do not have adequate written description.

17. Claim 52 is rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for methods of purifying epothilones that comprise epothilone D, does not reasonably provide enablement for methods of purifying only epothilone D. The instant rejection is set forth against Claim 52 as if it clearly required purifiation of only epotihlone D. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. To purify epothilone D to homogeneity would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in

Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

While the instant specification teaches very effective purification methods for epothilone D, 100% pure epothilone D (i.e., purifying only epothilone D using the purification methods disclosed) is not described (see page 143, paragraph 381). The specification presents no guidance or working examples for the absolute purification of epothilone D. Moreover, in the practiced methods, epothilone D must be purified from other epothilones, which is an arduous task as mentioned in the introduction of the instant specification. One of skill in the art would be wholly unable to predict additional purification steps for the production of only epothilone D using the instant methods. Thus, the instant application does not enable the full extent of the claimed scope.

18. Claim 54 is rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for methods of culturing epothilone-producing *M. xanthus* cells using methyl oleate as the carbon source, does not reasonably provide enablement for methods of culturing other epothilone-producing cells using methyl oleate as the carbon source D. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The culture any epothilone-producing cell on methyl oleate effectively would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized above.

The instant specification describes extensive studies on media development for the growth of *M. xanthus* K111-40-1, an epothilone D producing host cell (see pages 111-113). While this work is highly useful in the effective production of epothilone using K111-40-1 cells, it is not predictive of the ability of other cells, particularly non-*M. xanthus* cells, to grow on methyl oleate. No working examples or guidance for the culturing of non-*M. xanthus* cells is described in the specification. Thus, the instant claim is not enabled to the full extent of its scope.

19. Claim 59 is rejected under 35 U.S.C. § 112, first paragraph, enabling deposit, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. To practice the instant methods, one of skill in the art is required to use K111-40-1 cells. While the instant specification contains all deposit information on page 186,

the requirements to enable such a deposit have not been fully met by the instant application. To enable the instant claims by enabling the deposit of K111-40-1 cells, the record must contain a statement certifying that all restrictions on accessibility to said deposit be irrevocably removed by Applicant upon the granting of the patent (see M.P.E.P. § 2404.01); this statement may be certified by Applicants or Applicants' representative.

20. Claim 65 is rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for methods of culturing epothilone-producing *M. xanthus* cells, does not reasonably provide enablement for methods of culturing *M. xanthus* cells that do not produce epothilone. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The culture any *M. xanthus* to produce epothilone would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized above.

M. xanthus cells do not natively produce epothilone; said cells must be transformed with a complete, exogenous epothilone PKS gene cluster which encodes proteins for the biosynthesis of epothilone. If *M. xanthus* cells without such a gene cluster were the starting material for the claimed methods, no epothilone would be produced and no epothilone could thus be purified. No working examples or guidance of using such *M. xanthus* cells is described in the instant specification. Thus, the instant claim is not enabled to the full extent of its scope.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

21. Claims 40, 48, 49, 51, 55, 60, and 61 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hofmann *et al.* (WO 99/42602) in view of Reichenbach *et al.* (Biologically active secondary metabolites from myxobacteria. Biotechnol. Adv (1993) 11(2):219-277). The instant claims are drawn to purifying epothilone from *S. cellulosum* host cells by culturing the cells with XAD-16 resin and trace metals, eluting epothilone from said resin, performing solid phase extraction followed by C18 resin chromatography on said epothilone eluate, and crystallizing epothilone.

Hofmann *et al.* teach purification of epothilones using *S. cellulosum* cell culture that is combined with XAD-16 resin after culturing. Hofmann *et al.* further teach eluting epotihlone from the XAD-16 resin and subjecting said eluate to further extractions/columns chromatography steps (see pages 9-10); said further extractions/columns include C18 columns. Hofmann *et al.* also teach crystallization of epothilone at the end of the purification (see page 10 and page 38).

Hofmann *et al.* do not teach culturing *S. cellulosum* directly with the XAD-16 resin nor do they teach adding trace metals to the culture medium.

Reichenbach *et al.* teach culturing myxobacteria directly with XAD-16 resin in the fermentation as a way of stabilizing the secondary metabolites of the myxobacteria in large-scale

production (see page 252). Reichenbach *et al.* also teach the usefulness of adding Ca^{2+} and/or Zn^{2+} to *Sorangium* culture fermentations (see page 254).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Hofmann *et al.* and Reichenbach *et al.* because both references teach effective purification of epothilones from *S. cellulosum*. One would have been motivated to combine the teachings to practice the methods of Hofmann *et al.* using the modifications of Reichenbach *et al.* because effective large-scale purification is commercially desirable (see Hofmann *et al.*, page 2). One would have had a reasonable expectation of success that the combination of methods from Hofmann *et al.* and Reichenbach *et al.* would effectively purify epothilones because both method schemes had been tested by their respective references and nothing in said schemes is know to counteract the effectiveness of the other's method steps. Thus, Claims 40, 48, 49, 51, 55, 60, and 61 are obvious in view of the art.

Other Art for the Record

22. The Examiner makes the following art of record:

a) Hardt *et al.* New Natural Epothilones from *Sorangium cellulosum*, Strains So ce90/B2 and So ce/90/D13: Isolation, Structure Elucidation, and SAR Studies. J. Natural Products (June, 2001) 64(7): 847-856. Not prior art.
b) Arslanian *et al.* Large-Scale Isolation and Crystallization of Epothilone D from Myxococcus xanthus Cultures. J. Natural Products (2002) 65:570-572. Not prior art.
c) Lau *et al.* Optimizing the Heterologous Production of Epothilone D in *Myxococcus xanthus*. Biotechnol Bioeng. (2002) 78(3):280-8. Not prior art.
d) USPN 6,562,795 (Ashley *et al*) teaches using HP20SS and C18 columns for purification of FK-520, a related polyketide; this reference is not available as prior art since its priority document (60/183,338) does not teach using said columns.

Conclusion

23. Claims 40 and 48-65 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (571) 272-0931. The examiner can normally be reached on Monday through Friday, from 9:00am to 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kathleen M Kerr
Examiner
Art Unit 1652

March 22, 2004